REMARKS

I. Disposition of the claims and support for the amendments thereto

Claims 4, 6, 15, and 16 are cancelled.

Claims 1-3, 5, and 19-22 are amended and new claim 24 is added.

Claims 1-3, 5, and 19-24 are pending. A complete copy of all pending claims is attached hereto.

Support for the amendment for claim 2 is found in the specification, as originally filed, at pages 15 and 16.

II. Objection to the specification

The Examiner has objected to the specification as being informal because the "Description of the Drawings" is not labeled as such. The Examiner asserts that an improper attempt to correct this defect was made in a previous paper.

In response to the Examiner's objection the Applicant has outlined a remedial amendment as described above. Additionally, Applicant provides herewith substitute pages 7, 7A and 31, which incorporate the amendment, also enclosed are copies of the pages as originally filed with the amendments indicated in red ink.

III. Objection to the claims

The Examiner has objected to claims 1-3 and 5 as being informal for failing to commence with an article.

Upon entry of the claim amendment described above, claims 1-3 and 5 now each commence with an article. Consequently, Applicant requests that this objection be withdrawn.

IV. Rejection under 35 U.S.C. § 112, first paragraph

Claim 2 is rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled by the specification. Applicant respectfully traverses.

In view of the above amendment, Applicant asserts that claim 2 is fully supported by the specification. Applicant believes that the definitions outlined on pages 15 and 16 of the

specification clearly enable an artisan of ordinary skill to make the claimed invention. The specification explicitly recites that:

> [t]he term analog as used throughout the specification or claims to describe the proteins or peptides of the present invention, includes any protein or peptide having an amino acid residue sequence substantially identical to a sequence specifically shown herein in which one or more residues have been conservatively substituted with a biologically equivalent residue.

(Specification page 15, lines 8-12). The specification then proceeds to specifically set forth which amino acid substitutions are compatible with the instant invention (see Table 4, bridging pages 15 and 16).

From this description, it would be clear to an artisan of ordinary skill that an "analog" is a peptide which has an amino acid sequence identical to the respective SEQ ID NO except that one or more amino acid residues have been replaced with a biologically equivalent residue.

The Examiner has also alleged that the specification is "silent on what percentage of divergence is required to be considered an analog (see page 3 of the Office Action). Applicant respectfully disagrees. The Examiner's attention is directed to the passage, cited above, where in use of the phrase "*one or more residues have been conservatively substituted*" explicitly teaches that a peptide which diverges by even one amino acid residue is considered to fall within the scope of the term analog.

On page 4 of the instant Office Action the Examiner also alleges that the Applicant has failed

> to disclose what biochemical/immunological properties must be present in order for a peptide to be considered an "analog". Consequently, it would be impossible for one of skill in the art to ascertain what would fall under the category "analog."

Applicant respectfully agrees with this assessment.

Taken together with the above description from the specification, claim 1, as originally filed, clearly provides the additional characteristics needed to enable an artisan of ordinary skill to ascertain whether or not a peptide fell within the scope of claim 2. Claim 1 limits the "analogs" to peptides which have at least one arginine residue which is mono- or di-methylated.

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Furthermore, claim 1 restricts the claimed peptides to those which react with antibodies present in the sera of patients afflicted with systemic lupus erythematosus, mononucleosis, or cancers associated with Epstein-Barr virus infection. Applicant asserts that these limitations clearly convey to one of ordinary skill in the art how to determine whether or not a peptide falls within the scope of claim 2.

V. Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-3, 5, and 19-23 are rejected as allegedly being indefinite. Applicant respectfully traverses.

A. Claims 1-3 and 5

Claim 1 is rejected as allegedly being indefinite for its use of the terms "asymmetrical dimethyl arginine" and "symmetrical dimethyl arginine" as well as for the use of parentheses. As indicated in the instructions above, claim 1 is amended to eliminate the parentheses and replace them with commas. This is done in order to clarify the distinction between "symmetrical" and "asymmetrical" dimethyl arginine.

Applicant notes that, as used throughout the specification and the claims, the term "methylated arginine" is used in a broad sense to refer to both mono- and di-methylated arginine. In view of the specification and the claims, Applicant asserts that the meaning of "symmetrical" and "asymmetrical" are readily apparent to one of ordinary skill in the art. At page 8, lines 27-30 the specification recites:

> [a]ccording to its main embodiment the present invention relates to peptides that contain arginine residues that are immediately followed by a glycine residue, and wherein at least one arginine residue is methylated or dimethylated at one terminal amino group of the guanidino-group of the arginine residue.

Additionally, referring to the methylated peptide, page 12, lines 12-13 of the specification recite "wherein at least one and preferably each arginine is methylated, preferably dimethylated and even more preferably dimethylated in an asymmetric way." Finally, as amended, claim 1 now recites "wherein X stands for a N^G-mono- or N^G-N^G-dimethylated arginine, asymmetrical dimethyl arginine, or N^G-N'^G-dimethylated arginine, symmetrical dimethyl arginine." It is clear

from these passages that the methylation occurs on the terminal amino group on an arginine side chain. Applicant further asserts that, in view of these passages, it would be clear to an artisan of ordinary skill that "asymmetrical" dimethylation refers to the situation where both substituent methyl groups are bonded to the same nitrogen atom, whereas "symmetrical" dimethylation refers to the situation where there is on substituent methyl group on each of the terminal amino groups. This is particularly made clear by the notation used in claim 1, where "N^{G}-$N^{'G}$" refers to symmetrical dimethylation and "N^{G}-N^{G}" refers to asymmetrical dimethylation, with " N " denoting one of the terminal nitrogen atoms and " N' " denoting the second terminal nitrogen atom of the arginine guanidino group. In view of the foregoing explanation, Applicant believes that the rejection of claim 1 and its dependent claims, 2, 3, and 5 have been overcome.

B. Claim 19

The Examiner has rejected claim 19 as allegedly being indefinite due to the use of the phrases "such as" and "can be implicated." As amended the objectionable phrases are no longer part of claim 19. Applicant, therefore, requests that this rejection be withdrawn.

C. Claim 20

Claim 20 is rejected as allegedly being vague and indefinite for the use of the phrases "attached to specific locations" and "range of peptides." As amended the objectionable phrases are no longer part of claim 20. Applicant, therefore, requests that this rejection be withdrawn.

D. Claim 21

Claim 21 is rejected as allegedly being vague and indefinite for the use of the phrase "in the form of parallel lines." As amended the objectionable phrase is no longer part of claim 21. Applicant, therefore, requests that this rejection be withdrawn.

E. Claim 22

Claim 22 is rejected as allegedly being vague and indefinite for the use of the phrase "certain peptides." As amended the objectionable phrase is no longer part of claim 22. Applicant, therefore, requests that this rejection be withdrawn.

VI. Rejection under 35 U.S.C. § 102(e)

Claims 1, 2, 19, 20, and 23 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Hiepe *et al.* (U.S. Patent 5,945,105). Applicant respectfully traverses.

> Regarding anticipation under § 102 the courts have held that:
> anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference....In addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public.

Azko N.V. v. U.S. International Trade Commission, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987). Applicant asserts that, under the standard for anticipation set out in *Azko*, Hiepe *et al.*, does not anticipate the instantly claimed invention. All of the rejected claims recite that the claimed peptides must comprise a methylated arginine. In violation of the *Azko*, standard Hiepe *et al.* does not disclose the use of peptides containing methylated arginine residues. Consequently, Hiepe cannot anticipate any of the rejected claims. Accordingly, applicant respectfully requests that this rejection be withdrawn.

VII. Rejection under 35 U.S.C. § 103

Claims 1-3, 5, 19-21 and 23 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Rokeach *et al.* (1988) (PNAS 85:4832-4836, 1988) in view of Rawal *et al.* (Biochemica et Biophysica Acta 1248:11-18, 1995). Applicant respectfully traverses.

Regarding the standard for establishing a *prima facie* case of obviousness MPEP 706.02(j) provides, in pertinent part that:

> [t]o establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added).

The Examiner has noted that Rokeach *et al.* describes the sequence for an Sm-D autoantigen and the sequence of an Sm-D peptide (119 amino acids), which comprises SEQ ID NO: 1, with SEQ ID NO: 1, representing part of the sequence near the carboxy-terminal end of the peptide. Furthermore, the Examiner points out that Rokeach *et al.* speculates that the "(Gly-Arg)$_9$ repeated motif may constitute one of the Sm-D immunoreactive determinants" (see abstract, emphasis added). The Examiner has further noted that Rawal *et al.* describes a method for generating methylated peptides. Finally, the Examiner has alleged that "it would have been obvious for one of skill in the art to apply the methodology disclosed by Rawal et al. to generate and test human Sm-D auto antigen peptides that could be used in testing for Lupus erythematosus." (Page 7 of the instant Office Action). Applicant respectfully disagrees.

Applicant asserts that, contrary to the requirements of *Vaeck* there is no teaching or suggestion for combining the references to provide the instantly claimed invention. Furthermore, the combination of the prior art references provides not "reasonable expectation" of success.

While it is true that Rawal *et al.* suggests that methylated arginine is "commonly observed [when] these residues are present in glycine-and-arginine rich motifs." (See abstract). However, this is not equivalent to saying that glycine-and-arginine motifs are frequently methylated. Applicant asserts that this description in the Rawal *et al.* reference does not suggest that glycine-and-arginine are always or even frequently methylated. It only indicates that when arginine methylation does occur it often in a glycine/arginine rich area. Furthermore, Rawal *et al.* specifically indicates that methylation is only one of "many posttranslational modifications" which proteins may undergo (see page 11). Finally, in the conclusion of the Rawal *et al.* reference the authors teach that the function of "methylation is not known" (page 18). The authors then speculate that methylation may somehow modulate the proteins nucleic acid binding properties.

Rokeach *et al.* (1988) suggests that the 9-fold Gly-Arg repeat is located at the C-terminus, may "constitute one of the Sm-D immunoreactive determinants." (*See* abstract). Additionally, Rokeach *et al.* (1988) posits that these repeated Gly-Arg residues have the potential to form a series of β-turns (p. 4834). Furthermore, in Rokeach *et al.* (1992) (*Clin.*

Immun. and Immunopath., 35:315-324, 1992, a copy of which is included herewith as part of a Supplemental Information Disclosure Statement) the authors describe a further attempt to identify the immuonoreactive domains of the Sm-D autoantigen. The conclusions reached in Rokeach *et al.* (1992), are that the antibodies which recognized the Sm-D antigens either recognized (i) a conformational, or discontinuous, epitope which required folding of the peptide into its native conformation (requiring the use of a full-length peptide); or (ii) a "supercharged structure." (*See* pages 321-322).

Thus there is nothing present in the cited art which teaches or suggest that methylation is an feature which is crucial to antibody-antigen interaction. Instead, the cited art emphasizes three-dimensional structure and/or electrostatic charge as being of paramount importance. The teaching that methylation is critical to protein/antibody interaction is taught and claimed only by the application. Thus contrary to the teaching of *Vaeck* the cited references provide no motivation to combine their teachings in order to provide the instantly claimed invention.

Furthermore, the cited references do not render the instant invention obvious. As indicated in MPEP 2145 (X)(b) the standard is not "obvious to <u>try</u>," instead the standard is "obvious to <u>succeed</u>". In support of this view the Circuit Court of Patent Appeals has stated that:

> we have criticized the "obvious to try" test on several recent occasions....
>
> Furthermore, application of the "obvious to try" test would often deny patent protection to inventions growing out of well-planned research which is, of course, guided into those areas in which success is deemed most likely. These are, perhaps, the obvious areas to try. But resulting inventions are not necessarily obvious. Serendipity is not a prerequisite to patentability. Our view is that "obvious to try" is not a sufficiently discriminatory test.

In re Lindell, 155 USPQ 521, 523 (C.C.P.A. 1967). Given that the cited references do not even suggest that methylation may be important to peptide/antibody interaction, they cannot render the instantly claimed inventions obvious to "try." *A fortiori* the cited art cannot render the instant claims obvious to "succeed." In view of these arguments Applicant contends that the requirements of *Vaeck* are not met. Consequently, Applicant respectfully requests that the rejection of claims 1-3, 5, 19-21 and 23 under 35 U.S.C. § 103(a) be withdrawn.

VIII. Formal Drawings

As required by the Draftsperson, copies of Drawings 2-4, which comply with the requirements of 37 C.F.R. §1.84, are enclosed herewith.

IX. Conclusion

In view of the foregoing Amendment and Remarks, Applicant believes that all objections and Rejections of the instant Application have been overcome and that the case is now in condition for allowance.

The Examiner is invited to contact the undersigned attorney at (713) 787-1438 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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said solid support is a membrane strip and said polypeptides are coupled to the membrane in the form of parallel lines. It has to be understood that certain peptides, or antibodies as defined above, alternatively, are not attached to a solid support but are provided in the binding solution to be used as competitors and/or to block other antibodies that are present in sera from patients with autoimmune diseases other than SLE, thereby decreasing or eliminating possible cross-reaction and/or aspecific binding.

→ Insert lines 8 - 27 of page 31 of the Specification as filed (see attached sheet)

We have demonstrated for the first time that well defined secondary modifications (mostly N^G,N^G-dimethylarginine) are present on the Arg residues of the C-terminal peptide, that are followed by a glycine residue. Moreover, we have raised evidence that the C-terminal peptide can only show an immunoreactivity almost identical to the immunoreactivity of natural SmD, if these arginine residues are methylated. These dimethylarginines present on the nine Arg positions of the C-terminus, have been demonstrated for the first time in the natural SmD1 molecule. In SmD2 no dimethylarginine was retrieved while in the C-terminus of SmD3 the four RG motifs in the C-terminus again were found to be dimethylated.

The amino acid N^G,N^G-dimethylarginine is the result of a post-translational modification which seems to occur predominantly in RNA binding proteins (Najbauer, 1993). These nuclear proteins are enzymatically modified by a nuclear protein methylase I (S-adenosyl-methionine: protein-arginine N-methyltransferase, E.C.2.1.1.23; Rajpurohit, et al.,1994). The structural specificity of this enzyme seems to be an arginine containing peptide with glycine in the C-flanking position as was shown by substrate evaluation with synthetic peptides (Rawal, 1995). Nevertheless, in the same study it was demonstrated that the entire molecule also plays an important though thus far unknown role in the methylation process. Interestingly, this cellular methylation process can be mimicked *in vitro* with purified methylasel as was illustrated with recombinant heterogeneous nuclear RNP protein A1 (Rajpurohit,et al.1994)

From our results, we thus can conclude that in SmD immunoreactivity, at least 2 epitopes are involved. One of the epitopes is apparently present in the recombinant SmD1 molecule and can not be assigned to a linear epitope (epitope

immobilized on the membrane will preferentially be the methylated and unmethylated form of poly(Arg-Gly), combined with native and thus methylated SmD1 and/or SmD3 and/or Sm69, and unmethylated, recombinant SmD1 and/or SmD3 and/or Sm69.

Figure Legends

Figure1: HPLC profile of the Endo-Lys digest.

Figure 2: Immunodot of HPLC fractions with 5 patients sera and 1 control serum.

Figure 3: Immunodot of the C-terminal peptide (C-term mod) and without (C-term nt mod) dimethylarginine, and of the recombinant (baculo SmD, coli SmD) and natural protein (native). Strips were incubated with a anti-SmD positive serum (+) and a control serum (-). Total protein staining (Aurodyne) was performed on the third strip.

Insert at page 7 after line 7.

Figure 4: LIA with modified (dimethyl arginine) C terminal peptide (fraction 15 from EndoLys-C digest, line 1 on the strip), and non-modified C terminal peptide (fraction 8 from the EndoLys-C digest, line 2 on the strip), both applied in equal amounts (60 ng). Additionally, 7, 15 and 30 ng of recombinant SmD1 from baculovirus- or E. Coli-infected insect cells (resp. 4,5,6 and 7,8,9) as well as 15 and 30 ng of a mixture of gel-purified SmD (native) were applied to the strips. The total protein staining (Aurodyne) was performed on the first strip. The strips were incubated with (A) a panel of anti-SmD positive sera selected by INNO-LIA ANA from ANF-positive sera, (B) a panel of anti-SmD positive sera selected by INNO-LIA ANA from a cohort of SLE patients diagnosed according to the ACR criteria, (C) sera selected from MCTD patients (control panel) and (D) sera selected from ANF-negative sera (control panel). No reactivity was observed with sera from the control panels.

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